

### **REMARKS**

The Final Office action of February 25, 2009 has been carefully reviewed. It is regrettably noted that claims 22-23 are rejected under 35 U.S.C. § 103 (a) for the first time and yet the rejection is made final. It is utterly improper.

Claim 23 is currently amended so that it is believed that the § 112 rejection in the Final Office action is overcome.

Claim 22 is currently amended to narrow the claim to only a suspension formulation system based on hydrogenated castor oil and dimethicone. No new matter is introduced and no new search is necessitated as it only narrows the claim to a subject matter (hydrogenated castor oil and dimethicone combination) same as existing claim 23 in one aspect.

For the reasons stated in the following, Applicant respectfully disagrees with the rejection made under 35 USC § 103 (a) in the Final Office action.

### **The Invention**

The present invention for the first time provides an injection formulation based on a combinational use of hydrogenated castor oil as suspension agent and dimethicone as suspension medium, which solved the problems known in the art in terms of stability, fluidibility, injectability and long-lasting releasing effect (last paragraph, page 2 of the specification). Due to those known existing problems, all previous long-lasting injection formulations had proved to have little or no commercial value. The present invention surprisingly overcomes those problems with a suspension system, i.e., using hydrogenated castor oil/dimethicone as suspension agent/suspension medium, respectively, and it causes no side effects such as tissue damages, swelling, agglomeration, granuloma and it has an extremely long-lasting effect up to 110 days (paragraph 1, page 17 of the specification).

### **The Reference cited for §103(a) Rejection**

**The Chen reference** discloses an injection formulation of an avermectin compound with hydrogenated castor oil in a hydrophobic injection medium which dissolves the active ingredient and this injection formulation can provide a long release up to 42 days.

**The Yamahira reference** discloses an injection formation where the active ingredient does not dissolve in the injection medium but incorporated (or captured) in biodegradable particles which are then suspended in a viscous injection medium.

The two foregoing injection formulation systems clearly go in opposite directions. Chen requires the active ingredient be dissolved the medium while Yamahira prevents the soluble active ingredient from dissolving in the medium by capturing it with insoluble particles suspended in the medium.

Because the two references teach completely different systems, no reasonable person having ordinary skill in the art would believe that one can simply pick one element from one system, plug it into the other system and then expect it would work at all, much less with a better effect. It is a different factual situation from the one in the KSR case.

Thus, Applicant respectfully submits that the citation of the above references shows nothing more than the fact that some of the claimed elements are individually disclosed in separate prior art references and, as such, it cannot make a *prima facie* case of obviousness in the present case.

### **Legal Standard for Making *Prima Facie* Case of Obviousness**

To find an invention obvious requires that “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. Section 103(a). While rejecting a rigid application of the TSM test, the Supreme Court affirmed that it is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” KSR International Co. v. Teleflex Inc., 82 U.S.P.Q. 2d 1396 (2007).

A *prima facie* case of obviousness can be established by showing an apparent reason, either in the interrelated teachings of the references themselves, in the effects of demands in the design community or in the marketplace, or in the background knowledge possessed by a person having ordinary skill in the art, to combine the known elements in the fashion as claimed. As mandated by the Supreme Court in the KSR case, “this analysis [for finding the reason to combine known elements] should be made explicit,” citing *In re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006) (“[R]ejection on obviousness grounds cannot be sustained by mere conclusive statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”).

### **No Prima Facie Case Made in the Present Case**

The Examiner has failed to establish a *prima facie* case of obviousness because no articulated reasoning is presented with rational underpinning in combining the cited prior art references. No substantive, meaningful analyses were provided on any suggestion or motivation to combine the isolated elements from the separate references. There is nothing provided by the Examiner that goes beyond the statement that all the elements recited in the rejected claims can be found suitable and useful in separate formulation systems disclosed in scattered references (see the excerpts below from the Final office action).

**Rational and Motivation (MPEP 2142-43)**

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to add silicone oil (dimethicone) to the formulation of Chen et al. because Yamahira et al. teach silicone oil as a viscous solvent suitable for injection and Chen et al. teach that the viscous solvent creates a depot where the drug is slowly removed over a prolonged period of time. One of ordinary skill in the art would expect the viscous silicone oil would assist in forming the depot at the site of injection. Also, it would have been *prima facie* obvious to add an analgesic agent because Yamahira et al. teach that anesthetic agents are conventional pharmaceutical additives.

(second paragraph, page 5, final office action). The fact that Yamahira generally mentions "silicone oil as a viscous solvent suitable for injection" says nothing that would remotely suggest or motivate other to combine silicone oil in particular with hydrogenated castor oil to form a suspension system which will have a long-lasting effect up to 110 days, more than 2.5 times longer than the Chen system (45 days). It doesn't even provide any basis to believe that silicone oil would work if plugged in the Chen formulation. In fact, it does not work. Chen's system would require silicone oil dissolves the active ingredient and silicone oil cannot dissolve Chen's active ingredient (a fact on which the present invention is based). Thus, combining Chen and Yamahira is like combining a fire with water.

**Both References Actually Teach Away from Present Invention**

Not only is there no apparent reason to combine Chen with Yamahira, but also the references themselves teach away from the presently claimed invention. For its system with hydrogenated castor oil to work, Chen requires the injection medium must dissolve the inactive ingredient. Because silicone oil cannot dissolve the active ingredient (i.e., avermectin), it teaches away from using it.

The hydrogenated castor oil formulation contains the avermectin compound in a hydrophobic physiologically acceptable injection solvent in which the avermectin compound is readily soluble. Any physiologically and pharmaceutically acceptable carrier may be used so long as the avermectin compound is soluble therein. Examples of such carriers are glyceryl triacetate (Triacetin), distilled acetylated monoglycerides (Myvacet), miglyol 812, safflower seed oil and the like, or a combination of such carriers. The formulations

(lines 22-26, page 4, the Chen reference)

Avermectins are highly hydrophobic and hardly dissolvable in silicone oil, which is an important chemical basis for the avermectins to be prepared in long-lasting action formulations.

(paragraph 2, page 4, the present specification)

The Yamahira reference, on the other hand, promotes the use of biodegradable components and teaches away from using those that do not, particular the silicone products:

although a preparation using a non-biodegradable carrier such as silicone is recently used as a sustained-release preparation in some medical sections, it is not preferable because when it is administered in a parenteral route, there is a problem of accumulation of the carrier.

(line 24-29, column 1, the Yamahira reference)

### **The Claimed Subject Is Non-Obvious**

In view of the foregoing, Applicant respectfully submits that there is nothing in the references cited by the Examiner that renders the claimed subject matter obvious, which is an injection formulation based on a combinational use of hydrogenated castor oil and dimethicone, as a suspension agent and suspension medium, respectively, to form a long-term stable suspension system. Such a particular combinational system provides a long-lasting release up to 110 days. None of the cited references, alone or in combination, provides even a clue about this particular suspension system and this unexpected result of extremely long lasting release.

### **Conclusion**

Applicant respectfully submits that the rejection made under 35 USC103(a) in this case is improper. Reconsideration and allowance of the present application is earnestly solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to be 'G. Wang', written in a cursive style.

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George G. Wang, Ph.D., Reg. No.: 41,419  
Attorney for Applicant

Dated August 25, 2008  
georgewang@bei-ocean.com